



hepatitis B virus (HBV) who were matched for age and sex, and 30 healthy volunteers. Hypermethylated *RASSF1A* sequences were found in the serum of 93% of patients with HCC, 58% of HBV carriers, and none of the healthy individuals. The median *RASSF1A* levels for the patients with HCC and the HBV car-

riers were 770 copies/mL and 118 copies/mL, respectively, a finding consistent with previous studies showing that *RASSF1A* hypermethylation is an early event in HCC pathogenesis and can be found in premalignant liver tissues.

Using a cut-off of 300 copies/mL, this marker identified 82% of HCC cases

that were negative for α -fetoprotein, a known HCC marker. "If the 2 markers are elevated, it's very likely that a patient has liver cancer," said lead author K. C. Allen Chan. "It is possible that the 2 markers may be used synergistically to achieve better diagnostic accuracy," he added. □

Researchers Warm Up to Hypothermia Use After Cardiac and Brain Trauma

Tracy Hampton, PhD

FOR DECADES, MEDICAL RECOVERY stories of individuals who fell into icy waters or were buried under avalanches have left researchers intrigued by the beneficial effects of hypothermia. In some cases, people have survived in a comatose state without oxygen for lengthy periods of time without serious health effects.

Now, animal studies are revealing the potential of therapeutic hypothermia for treating myocardial infarction or brain injury, and researchers are developing elaborate, innovative cooling strategies.

SLURRY STUDIES

While oxygen deprivation resulting from cardiac arrest leads to tissue injury, even more damage can occur after a medical intervention has succeeded in restoring circulation. Laboratory studies by Lance Becker, MD, professor of emergency medicine at the University of Pennsylvania School of Medicine, in Philadelphia, and colleagues have found that most cells do not die when deprived of oxygen for several hours but rather are killed when oxygen is reintroduced. However, cooling immediately following myocardial infarction can suppress many of the chemical reactions associated with reoxygenation, or reperfusion, injury that lead to mitochondrial damage and apoptotic cell death.

But current methods for cooling patients, including external cooling devices such as cooling blankets and ice bags, are slow. "Our techniques of cooling are very primitive," said Becker, MD, who was named director of Penn's new Center for Resuscitation Science earlier this year. He and his team are conducting animal studies of a new approach that uses a novel cold slurry—a slushy mixture of salt and ice crystals—to achieve rapid cooling. When injected intravenously, this biocompatible solution drops internal temperature by 4°C within several minutes.

Eventually, the goal is to create a slurry delivery device that both trained and untrained individuals could use during an emergency. "Wouldn't it be great if you had something in your

house that would essentially put someone on ice?" asked Becker.

Other researchers, including Patrick Kochanek, MD, professor of anesthesiology and pediatrics in the department of critical care medicine at the University of Pittsburgh, in Pennsylvania, are investigating similar cooling solutions, such as intravenous iced saline. In studies in dogs, Kochanek and his team have tested their approach in conditions simulating resuscitating an individual who has experienced a myocardial infarction due to extensive loss of blood. They found that when they flushed an animal's body with a cold saline solution followed by resuscitation using cardiopulmonary bypass, neurological function could be recovered when resuscitation was initiated up to 3 hours after the infarction



Researchers are working to improve current methods of cooling patients during emergency situations such as heart and brain injury.



(Wu X et al. *J Cereb Blood Flow Metab.* doi:10.1038/sj.jcbfm.9600524 [published online ahead of print July 11, 2007]). “This has implications for transporting a combat casualty or a civilian trauma victim,” said Kochanek.

ONGOING RESEARCH

Understanding in detail how reperfusion injury occurs is a key area of Becker’s research, one that might lead to new types of interventions. “The goal is to figure out how to reintroduce oxygen without evoking the response that is harmful,” he said.

To that end, Becker and colleagues are investigating the biochemical steps that cause cell death during reperfusion in animals. They also are working on ways to extend brain function during periods of resuscitation. “It appears that one of the organs that is truly protected by this [slurry] technology is the brain and its long-term neurological functions,” he said.

Understanding the pathophysiology of reperfusion injury may also point to potential drug therapies. “If we know what hypothermia is affecting, maybe

we could develop drugs that target those mechanisms so that you wouldn’t need to cool,” said Kochanek. “Or we could add them to hypothermia to make it more beneficial,” he added.

Despite hypothermia’s potential benefits in emergency situations, cooling equipment is not routinely available on ambulances, said Becker, although he thinks that will change in the future as more information about the benefits of hypothermia becomes available. “We’re very early in this science, but the science looks very good,” he said. □

Study Probes Best Choice of Drug to Reduce Phosphate in Patients on Dialysis

Mike Mitka

A COSTLY AND WIDELY USED MEDICATION for patients on hemodialysis is no better at reducing mortality than lower-cost alternatives, according to the findings of a new study.

In the largest prospective randomized study to date comparing patients on hemodialysis who were given sevelamer hydrochloride (Renagel, Genzyme Corporation, Cambridge, Mass) or a calcium-based binder to treat hyperphosphatemia, the Dialysis Clinical Outcomes Revisited (DCOR) trial, researchers found that all-cause mortality was the same in the group taking sevelamer (267 deaths) and the group taking a calcium-based binder (275 deaths) (Suki WN et al. *Kidney Int.* doi:10.1038/sj.ki.5002466 [published online ahead of print August 29, 2007]).

However, in a prespecified secondary analysis of the trial (which was sponsored by Genzyme), the researchers did find a significant effect of sevelamer in lowering mortality rates based on age. The all-cause mortality rate in patients aged 65 years or older was 18.2 per 100 patient-years for those taking sevelamer and 23.4 per 100 patient-years for those taking a calcium-based binder.

There was a slight increase in mortality risk with sevelamer for those aged younger than 65 years, but it did not reach statistical significance.



Maintaining appropriate levels of phosphate is important for patients on hemodialysis, but the best way to do so remains open to debate.

GETTING RID OF PHOSPHATE

Patients with end-stage renal disease and those on hemodialysis often have hyperphosphatemia, which is a risk factor for cardiovascular calcification and cardiovascular morbidity and mortality. The

traditional therapy has been dietary intervention (advising patients to avoid foods high in phosphorus content) and administering a calcium-based binder to remove excess phosphates.

However, some have theorized that calcium-based binders could exacerbate hypercalcemia in patients on hemodialysis, which itself is a risk factor for cardiovascular calcification and its associated morbidity and mortality. If this is the case, a noncalcium binder such as sevelamer (which received US Food and Drug Administration approval in 1998 based on its ability to lower phosphate) should theoretically improve hyperphosphatemia without promoting hypercalcemia, thus reducing cardiovascular calcification and its effects.

Clinicians have been “treating patients with sevelamer more on belief than on evidence,” said Wolfgang C. Winkelmayer, MD, ScD, an assistant professor of medicine at Harvard Medical School, in Boston, who was not involved with the DCOR study. In light of the findings of this trial, he added, “I don’t think there’s a role for sevelamer in the treatment of hyperphosphatemia.”

Currently, Winkelmayer said, sevelamer is prescribed for about half of the US patients on hemodialysis (the National Institute of Diabetes and Digestive